Claim 33 has been amended to depend from claim 31. This amended dependence is supported in the specification, for example at page 5, lines 21-24.

Claims 65-68 have been added, are based on claims 5 and 35-38, as filed, and recite that the mutant HERG protein is MIRP protein. Use of MIRP is disclosed in the specification, for example at page 13, lines 15-21.

The Applicants respectfully contend that none of the amendments and additions made herein includes new matter.

Formal Drawings

The Applicants confirm receipt of the Notice of Draftperson's Patent Drawing Review. Formal drawings are enclosed with this Amendment. The Examiner is requested to confirm receipt of the formal drawings in the next communication to the Applicants.

Objection to Claim 33

Claim 33 stands objected to on the basis that, as filed, the claim recited dependence from itself. Claim 33 has been amended to depend from claim 31. This amended dependence is supported in the specification, for example at page 5, lines 21-24.

Rejection of Claims Pursuant to 35 U.S.C. § 112, First Paragraph

Claims 1-38 stand rejected pursuant to 35 U.S.C. § 112, first paragraph. The Examiner asserts that the specification does not provide enablement commensurate in scope with the claims. In support of this rejection, the Examiner recites numerous details of what is claimed and makes a variety of disparate observations that do not have any apparent relevance to enablement of the claimed invention. The Applicants respectfully contend that the Examiner has focused so narrowly on elements recited in dependent claims that she has overlooked the relative simplicity and elegance of the invention.

Greatly simplified, the Applicants' invention is that a mutant gene which is normally expressed only in an abnormal (e.g., diseased; see specification page 38, lines 14-17) tissue of an animal can be delivered to a second tissue in order to alleviate a different disease in that second tissue. The elements recited in the claim are i) a cell affected with a disease or disorder, ii) a gene therapy vector, iii) a promoter, and iv) a nucleic acid encoding a therapeutic

gene product that is usually only expressed in cells of an abnormal tissue that is not afflicted with the disease or disorder. The Applicants respectfully contend that each of these elements is known to the skilled artisan, and that once the skilled artisan is told that these elements should be combined in the manner set forth in the specification, the skilled artisan would not have any difficulty doing so. The Examiner's concerns appear to primarily involve whether or not the resulting method would be optimized, not whether it would be operable. The Applicants respectfully contend that there is no optimization requirement in the enablement requirement of 35 U.S.C. § 112, first paragraph. The Applicants need only teach the skilled artisan how to make and use the invention such that the method is operable. The Applicants respectfully contend that they have done so, and that the Examiner's concerns regarding how best to perform the claimed methods are irrelevant to enablement.

Among the things that are taught in the specification that were not previously known in the art is that the therapeutic gene that is delivered to cells is a gene that is normally only expressed in an abnormal tissue. The skilled artisan would not deliver such genes to diseased cells prior to the Applicants' disclosure of the usefulness of this method, as set forth in the specification at page 8, line 28, through page 9, line 2. In order to use the claimed methods, the skilled artisan needs to select an appropriate therapeutic gene to be delivered to the diseased cells. As set forth in the specification, at the paragraph bridging pages 13 and 14, many such genes are known, and it is within the ordinary level of skill in the art to select such a gene. The Examiner has not provided any evidence that the skilled artisan would be unable to select an appropriate therapeutic gene.

In order to use the methods recited in the pending claims, the skilled artisan also needs to make a gene therapy vector comprising the gene operably linked with a promoter. The Applicants respectfully contend that, given the state of the art, the skilled artisan was able to make various gene therapy vectors at the time the invention was made. Numerous examples of such vectors are recited in the specification at page 19, lines 6-13. The Examiner has not provided any evidence that the skilled artisan would be unable to generate a gene therapy vector comprising the selected therapeutic gene.

Finally, the claimed methods involve locally delivering the gene vector to affected cells in an animal. As disclosed in the specification at page 14, lines 8-18, and at page 20, line 22, through page 22, line 15, numerous methods that were known in the art when the invention

was made can be used to effect localized delivery of the gene in the gene vector. The Examiner has not provided any evidence that the skilled artisan would be unable to locally deliver a gene therapy vector.

The Applicants respectfully contend that the Examiner has not met her burden for rejecting claims pursuant to 35 U.S.C. § 112, first paragraph. The Examiner's burden is not merely to be able to formulate questions regarding if, or how well, the claimed methods may work. Instead, the Examiner must establish a reasonable basis to question the enablement provided for the claimed invention. M.P.E.P. §2164.04. The Examiner must provide reasoning or evidence that the skilled artisan, having access to the specification and what was known in the art at the time the invention was made, are unable to make or use the invention in a manner commensurate in scope with the claims. The Applicants respectfully contend that the Examiner has not met this burden.

There is no immediately evident thread of logic to the observations and assertions made by the Examiner in connection with the rejection of the claims pursuant to 35 U.S.C. § 112, first paragraph. However, in an attempt to be as responsive as possible, the Applicants attempt to respond to the Examiner's observations and assertions in the following paragraphs.

The Examiner's summary of what is claimed, at pages 3 and 4 of the Office Action, appears to be at least roughly accurate.

In the paragraph spanning pages 4-6 of the Office Action, the Examiner appears to raise several issues, which are addressed in the following bullet points.

- The Examiner appears to suggest that the data presented in Examples 1 and 2 merely pertain "only" to optimization of vector delivery, citing page 52 of the specification (evidently at lines 20-23). The Applicants note that the analyses presented in these examples are not disclosed as having such a limited purpose, as set forth, for example, at least at page 52, lines 23-26.
- Second, the Examiner appears to suggest that demonstrating expression of a mutant HERG gene in vitro in cultured cells or tissue sections is not predictive of alleviation of re-entrant atrial flutter or atrial arrythmia in vivo. The Examiner misunderstands the burden of rejecting claims pursuant to 35 U.S.C. § 112, first paragraph. As set forth in the M.P.E.P. (see, e.g., § 2164.04), the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed

invention. The Applicants suggest that the Examiner has done nothing more than merely question the Applicants' assertion of the operability of the claimed method. This is not a "reasonable basis," and the Examiner is not permitted to reject claims merely because a question regarding their operability can be formulated. There must be evidence or sensible argument presented that would cause a skilled artisan to question whether the claimed invention can be made and used.

- Third, the Examiner appears to question whether therapeutic levels of a mutant HERG protein could be expressed in vivo, even if the nucleic acid encoding the HERG protein is operably linked with a CMV or cardiac-specific promoter. The Applicants note, first, that a "therapeutic level" of expression is not recited in any pending claim, and second, that the skilled artisan understands that, at least for many therapeutic genes, there is no absolute minimum "therapeutic level." Instead, as with reducing myocardial conductivity, even relatively low levels of expression can alleviate a disease or disorder, even though relatively greater, better, or longer levels of expression might further alleviate the disease or disorder.
- Fourth, the Examiner appears to question whether any therapeutic effect could be achieved by expressing a mutant HERG protein in vivo in a patient afflicted with re-entrant atrial flutter or atrial arrythmia. Once again, the Examiner has provided no basis for questioning efficacy of mutant HERG gene expression. The Examiner is reminded that, in order to make an appropriate rejection pursuant to 35 U.S.C. § 112, first paragraph, the Examiner must provide a reasonable basis for a skilled artisan to question the enablement of what is claimed. The Applicants respectfully contend that the Examiner has not done so.

In the paragraph bridging pages 6 and 7, the Examiner cites unpredictability regarding the level and duration of gene expression that are achieved in gene therapy methods. The Applicants reply that these considerations are immaterial, for the simple reason that the claimed methods do not recite any particular level or duration of gene expression. It is sufficient to achieve only transient, low-level expression of a therapeutic gene, at least for certain diseases and disorders, as would be understood by the skilled artisan. Because the Applicants have not claimed any particular level or duration of gene expression, the Examiner's observations

regarding what is disclosed in certain older gene therapy references is irrelevant to enablement of what is claimed.

In the paragraph bridging pages 7 and 8 of the Office Action, the Examiner suggests that the art does not teach that mutant HERG proteins have therapeutic effect when expressed in cells. The Applicants respectfully contend that this observation is irrelevant. The Applicants have asserted that expression of a mutant HERG protein is useful for alleviating re-entrant atrial arrythmia and flutter. The Examiner has not, as she must pursuant to 35 U.S.C. § 112, first paragraph, provided evidence or reasoning that would cause the skilled artisan to doubt the Applicants' assertion. In the absence of such evidence, the Examiner is required to accept the Applicants' assertion as true.

The only full paragraph on page 8 of the Office Action appears to merely summarize several of the preceding paragraphs, and no response is believed necessary beyond that provided above.

In the paragraph bridging pages 8 and 9, the Examiner suggests that the dog atriotomy model is not predictive of all diseases in all animals. Stated in this form, this seems self-apparent, but irrelevant. The dog atriotomy model disclosed in an example in the specification is a model of re-entrant atrial flutter in humans, as disclosed at page 41, lines 12-15. It is not, nor is it intended to be, a model of all diseases in all animals. The Applicants once again remind the Examiner that they are not required to prove to the Examiner that the claimed invention is enabled. Instead, the Examiner is required to prove that the claimed invention is not enabled. Observing that a dog atriotomy model of atrial flutter is nor representative of all diseases in all animals proves nothing. The Examiner is requested to either address enablement of what is claimed or to withdraw the enablement rejection.

The Applicants believe that the only full paragraph on page 9 and the first full paragraph on page 10 of the Office Action merely recapitulate the pages that preceded them, and that these issues were fully responded to in the preceding paragraphs.

In summary, the Applicants respectfully contend that the Examiner has failed to meet the burden of providing evidence or sensible argument that would lead the skilled artisan to conclude that the Applicants have failed to teach how to make and use what is claimed. Reconsideration and withdrawal of the Examiner's rejection of claims 1-38 pursuant to 35 U.S.C. § 112, first paragraph, are respectfully requested.

Rejection of Claims Pursuant to 35 U.S.C. §112, Second Paragraph

Claims 22 and 33-38 stand rejected pursuant to 35 U.S.C. § 112, second paragraph.

The Examiner objects to the form of claim 22, suggesting that the elements listed in the alternative in originally claim must be recited in a typical Markush format. Although the Applicants believe that claim 22, as filed, properly and non-ambiguously listed the alternative elements, the Applicants have complied with the Examiner's suggestion by inserting "the group consisting of" before the alternative elements. The Applicants believe that this amendment does not alter the meaning of the claim in any way, and that the amended claim 22 should be recognized by the Examiner as being in proper alternative format.

The Examiner rejected claims 33-38 on the grounds that claim 33, as filed, improperly depended on itself, and that claims 34-38 depended from that improperly formatted claim. The Applicants have amended claim 33 to depend from claim 31, and respectfully contend that each of claims 33-38 is in compliance with the second paragraph of 35 U.S.C. § 112.

Reconsideration and withdrawal of the Examiner's rejection of claims 22 and 33-38 pursuant to 35 U.S.C. § 112 are respectfully requested.

Rejection of Claim 39 Pursuant to 35 U.S.C. § 102(b)

Claim 39 stands rejected pursuant to 35 U.S.C. § 102(b) in view of Sanguinetti.

Claim 39 has been canceled. Therefore, the Examiner's rejection is moot.

Summary

For the reasons set forth above, the Applicants respectfully contend that each of the Examiner's rejections either has been overcome or is inapplicable to the pending claims. Claims 1-38 and 65-68 are therefore believed to be in condition for allowance. Reconsideration and withdrawal of the Examiner's rejections and allowance of the pending claims are requested at the earliest possible time.

Respectfully submitted,

Robert J. Levy *et al.*

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(Date)

By: _____

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Enclosures: Petition for Extension of Time
Transmittal of Formal Drawings
10 Sheets of Formal Drawings